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EXAMINER	
DUNSTON, JENNIFER ANN	
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1636	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/055,711	REBAR ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,22-28 and 30-61* is/are pending in the application.

4a) Of the above claim(s) *1,3,5,23,24,33-35,38 and 42-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,22,25-28,30-32,36,37,39-41 and 53-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 10/17/2006, in which claims 6-21 and 29 were canceled; claims 32, 41, 52 and 53 were amended; and claims 56-61 were newly added. Currently, claims 1-5, 22-28 and 30-61 are pending.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Election/Restrictions

Applicant elected Group II (drawn to nucleic acid), species: DNA target sequence, zinc finger component comprising X(3)-Cys-X(2)-Cys-X(12)-His-X(3)-Z-X(4), target located in a plant cell, and a maize C1 activation domain in the reply filed on 8/3/2004 and 11/18/2004. This restriction requirement was made FINAL in the Office action mailed 2/9/2005 and reiterated in the Office action mailed 11/15/2005. Applicant's arguments regarding rejoinder have been fully considered but are not persuasive for the reasons of record.

The requirement for the election of a specific zinc finger component, as set forth on pages 3-4 of the Office action mailed 7/1/2004 withdrawn in the Office action mailed 6/14/2206. The remainder of the species election requirement was maintained in the Office action mailed 6/14/2006. Thus, the species election requirement for target sequence type, where the target is located and functional domain type are maintained.

Claims 1, 33 and 42-52 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking

claim. Applicant timely traversed the restriction (election) requirement in the replies filed on 8/3/2004 and 11/18/2004.

Claims 3, 5, 23-24, 34-35 and 38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the replies filed on 8/3/2004 and 11/18/2004.

Currently, claims 2, 4, 22, 25-28, 30-32, 36-37, 39-41 and 53-61 are under consideration.

Response to Arguments - 35 USC § 101

The rejection of claims 32 and 41 under 35 U.S.C. 101 has been withdrawn in view of Applicant's amendment to the claims in the reply filed 10/17/2006.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 4, 22, 25-28, 30-32, 36-37, 39-41, 53-56 and 58-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was made in the

Office action mailed 11/15/2005 and has been rewritten to extend the rejection to new claims 56-61, which were added in the reply filed 10/17/2006.

Claims 2, 4, 22, 25-28, 30-32, 36, 37, 39-41 and 53-56 are drawn to an isolated polynucleotide encoding a non-naturally-occurring zinc-finger binding protein comprising a non-canonical zinc finger component, wherein said non-canonical zinc finger component contains a beta turn comprising the two amino-terminal cysteine or histidine zinc coordinating residues and an alpha helix comprising the two carboxy-terminal cysteine or histidine zinc coordinating residues, and at least one of the amino-terminal zinc coordinating residues is a histidine residue or at least one of the carboxy-terminal zinc coordinating residues is a cysteine residue and wherein the protein is engineered to bind to a target sequence. Thus, the claims are drawn to a genus of compounds that is defined by secondary structure (beta turn and alpha helix), primary structure (cysteine and histidine zinc coordinating residues that differ from the canonical C2H2 consensus), and function in that they must be capable of binding to a target sequence. Claim 56 limits the zinc coordinating residues of the zinc finger of claim 30 to C_2HC or C_2CH. Given the structural limitations of the claims, the primary structure must be capable of providing the information necessary to allow the protein to fold into the recited secondary structures.

Claim 58 is drawn to an isolated polynucleotide encoding a non-naturally-occurring zinc finger binding protein comprising a non-canonical zinc finger component, wherein said non-canonical zinc finger components contains a beta turn comprising the two amino-terminal cysteine or histidine zinc coordinating residues and an alpha helix comprising the two carboxy-terminal cysteine or histidine zinc coordinating residues, wherein at least one of the amino-terminal zinc coordinating residues is a histidine residue or at least one of the carboxy-terminal

zinc coordinating residues is a cysteine residue, and wherein at least one of the zinc coordinating residues is a histidine. This structure excludes C_4 zinc fingers, but encompasses the following zinc fingers: HCH_2, CHH_2, C_2HC, C_2CH, and H_4. The primary structure must be capable of providing the information necessary to allow the protein to fold into the recited structure and must be capable of binding to a target sequence.

Claim 59 is drawn to an isolated polynucleotide encoding a non-naturally-occurring zinc finger binding protein comprising a non-canonical zinc finger component, wherein said non-canonical zinc finger component contains two amino-terminal zinc coordinating cysteine or histidine residues and two carboxy-terminal zinc coordinating cysteine or histidine residues, wherein at least one of the amino-terminal zinc coordinating residues is a histidine residue, or at least one of the carboxy-terminal zinc coordinating residues is a cysteine residue. This "zinc finger" can adopt any secondary structure. The formula provided by the claims encompasses zinc fingers that have the following zinc coordinating residues: C_4, HCH_2, CHH_2, C_2HC, C_2CH, and H_4. The primary structure must be capable of binding to a target sequence.

Claim 60 is drawn to an isolated polynucleotide encoding a non-naturally-occurring zinc finger binding protein comprising a non-canonical zinc finger component, wherein said non-canonical zinc finger component contains two amino-terminal zinc coordinating cysteine or histidine residues and two carboxy-terminal zinc coordinating cysteine or histidine residues, wherein at least one of the amino-terminal zinc coordinating residues is a histidine residue, or at least one of the carboxy-terminal zinc coordinating residues is a cysteine residue, and wherein at least one of the zinc coordinating residues is a histidine. This "zinc finger" can adopt any secondary structure. The formula provided by the claims encompasses zinc fingers that have the

following zinc coordinating residues: HCH_2, CHH_2, C_2HC, C_2CH, and H_4. The primary structure must be capable of binding to a target sequence.

Claim 61 is drawn to an isolated polynucleotide encoding a non-naturally-occurring zinc finger binding protein comprising a non-canonical zinc finger component, wherein said non-canonical zinc finger components contains a beta turn comprising the two amino-terminal zinc coordinating residues and an alpha helix comprising the two carboxy-terminal zinc coordinating residues, and the zinc-coordinating residues do not consist of two cysteine residues and two histidine residues. This claim encompasses the use of any combination of amino acids other than C_2H_2, and must be capable of binding a target sequence.

Thus, the claims encompass a very broad genus of isolated polynucleotides that encode proteins defined by either primary structure alone or a combination of primary and secondary structure, where the encoded protein is capable of binding a target sequence.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

In the instant case, while the claims contain a description of a general structure drawn to the non-canonical zinc finger component containing a beta turn comprising the two amino-terminal cysteine and histidine zinc coordinating residues and an alpha helix comprising the two carboxy-terminal cysteine and histidine zinc coordinating residues, the structure is further limited by excluding the C2H2 structure which supports that structure, instead claiming a retention of

the structure without use of the standard C2H2 zinc coordinating residues. In other words, what is claimed is a structure where the critical C2H2 residues, which are used to support the structure, have been replaced with amino acid residues that are not C2H2 (and whatever other amino acid changes are needed to support that replacement of the zinc coordinating residue(s)). While cysteine and histidine are both known to coordinate zinc atoms in the context of properly folded zinc fingers, these critical amino acids are not predictably interchanged (Green et al. Biochem J., Vol. 333, pages 85-90, 1998, cited in a prior action). For example, Green et al teach that the conversion of the C2H2 zinc fingers of Zif268 to C4 zinc fingers allows proper folding and function of the Zif268 zinc finger domains only if the mutation is present in zinc finger 1 or 3. In contrast, mutation of zinc finger 2 abolishes binding, which is likely a result of the inability of the protein to form the necessary secondary structure (e.g. Green et al, page 89, paragraph bridging columns). Furthermore, if zinc fingers 1 and 3 were simultaneously mutated, the protein was unable to bind DNA (e.g. Green et al, page 89, paragraph bridging columns). Thus, sequences other than the zinc coordinating residues play a role in determining the secondary structure and target sequence binding of the polypeptide. A review of the specification identified multiple examples of only one general type of non-canonical zinc finger protein meeting the claim limitations: a zinc finger protein in which the zinc coordinating residues are C2HC. There does not appear to be a description of any other zinc fingers that meet the claim limitations with regard to the zinc coordinating residues and secondary structure. Furthermore, the specification does not describe a structure function correlation for residues that support the formation of the claimed secondary structure when a zinc coordinating residue is altered. Accordingly, in the absence of sufficient recitation of distinguishing characteristics (e.g., specific sequences) drawn

to other types of non-canonical zinc fingers which retain the canonical structure using zinc coordinating residues that are neither C2H2 nor C2HC (the only structures whose sequences are specifically described), the specification does not provide adequate written description of the claimed genus which encompasses all non-canonical zinc fingers having the canonical general structure.

With regard to the recitation of "non-naturally occurring zinc finger binding protein," the specification does not describe which zinc fingers proteins are definitively non-naturally occurring because all natural proteins are not known. Further, natural proteins encompass proteins that result from mutations that naturally occur such as point mutations and chromosomal translocations. All of the proteins not previously described which are naturally occurring are simply unpredictable because, for example, such proteins encompass proteins from mutant genes. Further, some mutant genes may result from the fusion of DNA binding domains and regulatory domains to two different proteins. Accordingly, in the absence of sufficient recitation of distinguishing characteristics (distinguishing the isolated polynucleotide molecules that encode non-natural proteins from those that encode natural proteins), the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed

chemical structure of the encompassed genus of non-canonical zinc fingers as claimed, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or identification. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polynucleotides encoding a non-canonical zinc finger, wherein the zinc coordinating residues are drawn to the C2HC structure (and having the other claim limitations) but not the full breadth of the claims meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Response to Arguments - 35 USC § 112

The rejection of claim 53 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, has been withdrawn in view of Applicant's amendment to the claims in the reply filed 10/17/2006.

With respect to the rejection of claims 2, 4, 22, 25-28, 30-32, 36-37, 39-41, 53-56 and 58-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, Applicant's arguments filed 10/17/2006 have been fully considered but they are not persuasive.

The response essentially asserts that the claims exclude structures that do not bind DNA and do not adopt a ββα structure, and thus the ability of a protein to adopt such a conformation is immaterial to their written description. This is not found persuasive, because upon reading the specification, one would not know which primary amino acid sequences disclosed in the specification form the claimed secondary structure and have the claimed function. Given the unpredictability of predicting function from primary structure with regard to zinc finger proteins, evidenced by Green et al, one could not extrapolate from the examples provided in the specification to additional members of the genus that meet the claim limitations with regard to structure and function. Thus, specific guidance is what is required with regard to describing primary amino acid sequences that are capable of adopting the claimed secondary structure and providing the claimed function.

> "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004).

In the instant case, the specification describes zinc finger proteins that have the C_2HC structure. Description of this species of zinc finger does not predict the operability of other zinc fingers such as C_4, HCH_2, CHH_2, C_2CH, and H_4.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2, 4, 26-28, 30-32, 54, 59 and 61 are rejected under 35 U.S.C. 102(b) as being anticipated by Green et al (Biochem J., Vol. 333, pages 85-90, 1998; see the entire reference). This rejection was made in the Office action mailed 6/14/2006 and has been extended to address new claims 59 and 61.

Regarding claim 30, Green et al teach an isolated polynucleotide encoding a modified zif268 zinc finger binding protein, which contains a mutation of the C2H2 motif to a C4 motif in the first or third zinc finger (e.g. page 87, Results). In the C4 motif of Green et al, the zinc coordinating residues are two amino-terminal cysteine residues and two carboxy-terminal cysteine residues, and thus one of the carboxy-terminal zinc coordinating residues is a cysteine. The modified zif268 zinc finger binding proteins are engineered to bind to the wild type zif268 target DNA sequence 5'-GCGTGGGCG-3' (e.g. paragraph bridging pages 87-88; page 87, right column, 1st full paragraph; Figure 2, especially lanes c and e). Chen et al teach that the mutations allowed for proper folding of the zinc fingers to form a beta turn comprising two

amino-terminal zinc coordinating cysteine or histidine residues and an alpha helix comprising two carboxy-terminal zinc coordinating cysteine or histidine residues, which is indirectly evidenced by the ability of the expressed protein to bind DNA (e.g. paragraph bridging pages 88-89). Thus, Chen indirectly provides evidence that the modified zif268 proteins comprise a non-canonical zinc finger component that contains a beta turn and an alpha helix that coordinate zinc using the four cysteine residues.

Regarding claim 31, Green et al teach the Pharmacia pGEX-3X expression vector comprising the isolated polynucleotide (e.g. paragraph bridging pages 86-87; page 87, RESULTS).

Regarding claim 32, Green et al teach *Escherichia coli* bacterial strain BL21(DE3) comprising the expression vector (e.g. page 87, left column, 1st full paragraph).

Regarding claims 2, 4 and 27, the target sequence 5'-GCGTGGGCG-3' taught by Green et al is a DNA sequence consisting of 9 contiguous base pairs (e.g. paragraph bridging pages 87-88; page 87, left column, 2nd full paragraph, and right column, 1st full paragraph).

Regarding claim 26, Green et al teach the isolated polynucleotide, wherein the modified zif268 zinc finger binding protein contains three zinc finger components (e.g. paragraph bridging pages 87-88).

Regarding claim 28, Green et al teach the isolated polynucleotide, wherein the third zinc finger contains the C4 motif (e.g. paragraph bridging pages 87-88).

Regarding claim 54, Green et al teach the isolated polynucleotide, wherein the first zinc finger contains the C4 motif (e.g. paragraph bridging pages 87-88).

Regarding claim 59, Green et al teach an isolated polynucleotide encoding a modified zif268 zinc finger binding protein, which contains a mutation of the C2H2 motif to a C4 motif in the first or third zinc finger (e.g. page 87, Results). In the C4 motif of Green et al, the zinc coordinating residues are two amino-terminal cysteine residues and two carboxy-terminal cysteine residues, and thus one of the carboxy-terminal zinc coordinating residues is a cysteine. The modified zif268 zinc finger binding proteins are engineered to bind to the wild type zif268 target DNA sequence 5'-GCGTGGGCG-3' (e.g. paragraph bridging pages 87-88; page 87, right column, 1st full paragraph; Figure 2, especially lanes c and e).

Regarding claim 61, Green et al teach an isolated polynucleotide encoding a modified zif268 zinc finger binding protein, which contains a mutation of the C2H2 motif to a C4 motif in the first or third zinc finger (e.g. page 87, Results). In the C4 motif of Green et al, the zinc coordinating residues are two amino-terminal cysteine residues and two carboxy-terminal cysteine residues, and thus one of the carboxy-terminal zinc coordinating residues is a cysteine. The modified zif268 zinc finger binding proteins are engineered to bind to the wild type zif268 target DNA sequence 5'-GCGTGGGCG-3' (e.g. paragraph bridging pages 87-88; page 87, right column, 1st full paragraph; Figure 2, especially lanes c and e).

Claims 59 and 61 are rejected under 35 U.S.C. 102(b) as being anticipated by Miesfeld et al (Science, Vol. 236, pages 423-427, 1987, cited in a prior action; see the entire reference) as evidenced by Hard et al (Science, Vol. 249, pages 157-160, cited in a prior action; see the entire reference). This is a new rejection, necessitated by the addition of new claims 59 and 61 in the

reply filed 10/17/2006, specifically because new claims 59 and 61 do not specify the secondary structure elements of the previously presented claims.

Miesfeld et al teach an isolated polynucleotide encoding a non-naturally-occurring zinc-finger binding protein (polynucleotides, that encode mutants of the rat glucocorticoid receptor, such as the delta 70-130 mutant) (abstract; page 423, Figures 1-2 and throughout the reference). The encoded protein comprises one or more non-C2H2 zinc finger components (such as the hormone binding component which is a functional domain and the non-DNA binding domain components shown in Figure 1). The mutant protein reads on a protein engineered or designed to bind to a target sequence, because the mutant protein was designed to have the DNA binding domain, which binds to a particular sequence. The glucocorticoid receptor part of the fusion protein comprises a zinc finger of the C_4 type, as evidenced by Figure 1 of Hard et al, which shows the rat glucocorticoid receptor sequence. The target sequence for the mutant protein is the DNA sequence for glucocorticoid receptor, the glucocorticoid response element (GRE) (first column of page 423).

Hard et al is cited only as evidence that the teachings of Miesfeld et al inherently meet the claim limitations as shown by the cited teachings described above.

Claims 2, 4, 26-28, 30-32, 54 and 55-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Abeliovich et al (Molecular and Cellular Biology, Vol. 13, pages 7766-7773, 1993; see the entire reference). This is a new rejection, necessitated by the addition of new claims 56-61 in the reply filed 10/17/2006, specifically because new claims 56-58 and 60 exclude the C_4 zinc finger structure of the rejections of record.

Regarding claims 30 and 56-61, Abeliovich et al teach an isolated polynucleotide, $\lambda_{1\text{-}5/6}$, encoding a non-naturally occurring zinc-finger binding protein comprising a non-canonical zinc finger component of the formula CCHC, which was engineered (selected by an empirical process) to specifically bind to the UMS H strand sequence (e.g. paragraph bridging pages 7766-7767; page 7767, UMSBP fusion protein expression in bacteria; paragraph bridging pages 7767-7768; Figure 5). The polypeptide encoded by $\lambda_{1\text{-}5/6}$ is a non-naturally occurring fusion protein comprising CCHC zinc fingers and beta-galactosidase (e.g. page 7767, UMSBP fusion protein expression in bacteria; paragraph bridging pages 7767-7768). The mutant protein reads on a protein engineered or designed to bind to a target sequence because the mutant protein was designed to have the DNA binding domain, which binds to the UMS H sequence. Because the Office does not have the facilities for examining and comparing the applicant's product with the products of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product) (i.e. the CCHC zinc fingers of Abeliovich et al do not comprise a beta turn comprising two amino-terminal cysteines that coordinate zinc and an alpha helix comprising a histidine and a cysteine that each coordinate zinc). See *in re Best* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Regarding claims 2 and 4, the UMS H target sequence is a DNA sequence (e.g. page 7766, right column).

Regarding claim 26, the $\lambda_{1\text{-}5/6}$ polynucleotide of Abeliovich et al contains five CCHC zinc fingers and thus, comprises three zinc finger components (e.g. page 7767, UMSBP fusion protein expression in bacteria; paragraph bridging pages 7767-7768; Figure 4).

Regarding claim 27, the UMS H target sequence is 5'-GGGGTTGGTGTA-3', which is 12 contiguous base pairs (e.g. page 7766, right column).

Regarding claim 28, the third zinc finger encoded by the $\lambda_{1\text{-}5/6}$ polynucleotide is a non-canonical CCHC zinc finger (e.g. Figures 4-5).

Regarding claim 31, the $\lambda_{1\text{-}5/6}$ polynucleotide taught by Abeliovich et al is an expression vector (e.g. page 7767, UMSBP fusion protein expression in bacteria; paragraph bridging pages 7767-7768).

Regarding claim 32, Abeliovich et al teach an isolated *E. coli* cell comprising the $\lambda_{1\text{-}5/6}$ polynucleotide (e.g. page 7767, UMSBP fusion protein expression in bacteria).

Regarding claim 54, the first zinc finger encoded by the $\lambda_{1\text{-}5/6}$ polynucleotide is a non-canonical CCHC zinc finger (e.g. Figures 4-5).

Regarding claim 55, the zinc finger protein encoded by the $\lambda_{1\text{-}5/6}$ polynucleotide comprises four zinc finger components (e.g. Figures 4-5).

Claims 2, 4, 25-28, 30-32, 54 and 58-61 are rejected under 35 U.S.C. 102(a) as being anticipated by Hori et al (J. Am.Chem. Soc. Vol. 122, pages 7648-7653, published online 7/29/2000; see the entire reference). This is a new rejection, necessitated by the addition of new claims 56-61 in the reply filed 10/17/2006, specifically because new claims 56-58 and 60 exclude the C_4 zinc finger structure of the rejections of record.

Regarding claims 30 and 58-61, Hori et al teach an isolated polynucleotide encoding a non-naturally occurring zinc finger binding protein, H_4Sp1 comprising a non-canonical H_4 zinc finger component, which is engineered to bind to a GC box target sequence (e.g. page 7649, left column, paragraph 3; page 7649, right column, paragraph 5). The H_4 zinc finger component comprises a beta turn comprising two amino-terminal zinc coordinating histidine residues and an alpha helix comprising two carboxy-terminal zinc coordinating histidine residues (e.g. Figure 4).

Regarding claims 2 and 4, the target sequence bound by H_4Sp1 is a DNA sequence (e.g. page 7649, right column, paragraph 5).

Regarding claim 25, the "GC box" bound by H_4Sp1 is a promoter sequence (e.g. page 7649, right column, paragraph 5).

Regarding claim 26, the H_4Sp1 protein comprises three zinc finger components (e.g. page 7649, left column, paragraph 3).

Regarding claim 27, the target sequence is 5'-GGGGCGGGGCC-3' and comprises about 9 to 14 contiguous base pairs (e.g. paragraph bridging pages 7651-7652).

Regarding claim 28, the third zinc finger comprises a non-canonical H_4 zinc finger component (e.g. page 7649, left column, paragraph 3).

Regarding claim 31, Hori et al teach an expression vector encoding the H_4Sp1 protein (e.g. page 7649, left column, paragraph 3).

Regarding claim 32, Hori et al teach an isolated *E. coli* host cell comprising the expression vector (e.g. page 7649, left column, paragraph 3).

Regarding claim 54, the first zinc finger comprises a non-canonical H_4 zinc finger component (e.g. page 7649, left column, paragraph 3).

Response to Arguments - 35 USC § 102

With respect to the rejection of claims 2, 4, 26-28, 30-32, 54, 59 and 61 under 35 U.S.C. 102(b) as being anticipated by Green et al, Applicant's arguments filed 10/17/2006 have been fully considered but they are not persuasive.

The response asserts that Green et al do not teach each and every limitation of the rejected claims. Specifically, the response asserts that the specification defines the term "engineered" to indicate that a zinc finger protein can be engineered to bind a target sequence using design methods (based on rational criteria) or empirical selection processes such as phage display. The response points to page 10, lines 17-29 which states the following:

> A "modified" zinc finger protein is a protein not occurring in nature that has been designed and/or selected so as to comprise a substitution of at least one amino acid, compared to a naturally occurring zinc finger protein. Further, a "designed" zinc finger protein is a protein not occurring in nature whose structure and composition results principally from rational criteria. Rational criteria for design include application of substitution rules and computerized algorithms for processing information in a database storing information of existing ZFP designs and binding data, for example as described in co-owned PCT WO00142219. A "selected" zinc finger protein is a protein not found in nature whose production results primarily from an empirical process such as phage display. See e.g., US 5,789,538; U.S. 6,007,988; U.S. 6,013,453; WO 9511943 1; WO 96106166 and WO 9815431 1. Designed and/or selected ZFPs are also referred to as "engineered" ZFPs and can be modified according to the methods and compositions disclosed herein (e.g., by conversion to C3H and/or to comprise a plant backbone).

The specification states that "engineered" proteins are also referred to as "designed" or "selected" proteins. Thus, the genus of engineered proteins is broader than the definitions for "designed" and "selected" proteins. Furthermore, a "designed" protein is "a protein not occurring in nature whose structure and composition results principally from rational criteria." The rational criteria that are used are not defined explicitly. Although the specification sets forth

some examples of rational criteria, it is done in the context of "includes and encompasses" and thus the claim is not limited by those criteria. With respect to "selected" zinc finger proteins, the specification defines the proteins as one "not found in nature whose production results primarily from an empirical process." The specification does not explicitly define the empirical processes that result in the production of a selected zinc finger.

The specification asserts that the claim term "engineered" must be interpreted based upon its ordinary and customary meaning to a person of ordinary skill in the art at the effective filing date of the application, January 22, 2001. The remarks provide evidence that one would interpret the term "engineered zinc finger protein" to mean non-naturally-occurring zinc finger proteins having a binding specificity different from that of any naturally-occurring zinc finger protein, said binding specificity having been determined by the investigator by empirical selection methods or rational design methods. While the term would be interpreted to encompass that particular embodiment, one of skill in the art at the time the invention was made would also recognize the term to encompass other modifications to proteins. For example, Chapman et al (Engineering proteins without primary sequence tryptophan residues: mutant trp repressors with aliphatic substitutions for tryptophan side chains. Gene, Vol. 163, pages 1-11, 1995) teaches that proteins can be engineered to contain mutations and still bind the same DNA sequence (e.g. page 2, right column, paragraph 2). Further, Caporale (Lessons from the most innovative genetic engineer. Nature Biotechnology, Vol. 16, pages 908, 1998) teaches that although we used genetic engineering to modulate local nucleotide variation, rearrange genomic DNA sequences, and to acquire functional DNA sequences from the environment through horizontal gene transfer, we are not the first genetic engineers; nature works as a genetic engineer with a far richer palette

than random changes in nucleotides (e.g. page 908, left column, paragraph 1). Thus, the term "engineered" encompasses more than alteration of binding site specificity. Accordingly, one would recognize that the term "engineered" would encompass proteins that have been altered by site-directed mutagenesis, as taught by Green et al. It is noted that the features upon which applicant relies (i.e., the alteration in nucleotide binding specificity) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The response asserts that Green et al do not use rational criteria, because Green altered certain zinc-coordinating residues and tested the mutant proteins for their ability to bind the same target sequence. This is not found persuasive, because the definition set forth in the instant specification does not explicitly limit the changes in the protein to those that alter DNA binding specificity and other changes are encompassed by the claims. Green et al teach the use of rational criteria to design the zif268 zinc-finger motifs to non-native zinc-coordination sites, because Green et al understand that the cysteine and histidine residues of the zinc finger coordinate zinc ions and they alter these residues based upon their function in the wild-type protein to determine the interchangeability of these residues (e.g. pages 85-86, Introduction). The engineered zinc fingers that are capable of binding the wild-type DNA recognition element are selected based upon empirical observations using mobility-shift assays (e.g. page 87, Mobility-shift assays (MSAs); paragraph bridging pages 87-88). Therefore, the criteria used by Green et al to design the zinc finger proteins fall within the scope of rational criteria encompassed by the definition for "designed" zinc finger proteins and the empirical methods

encompassed by "selected" zinc finger proteins, each of which are encompassed by the term "engineered," as set forth in the specification and given the broadest reasonable interpretation as one of ordinary skill in the art would have recognized at the time the invention was made.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 25, 36 and 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Green et al (Biochem J., Vol. 333, pages 85-90, 1998; see the entire reference) in view of Pomerantz et al (Science, Vol. 267, No. 5194, pages 93-96, 1995; see the entire reference). This rejection was made in the Office action mailed 6/14/2006 and is reiterated below.

The teachings of Green et al are described above and applied as before.

Green et al do not teach the isolated polynucleotide further comprising an activation domain, wherein the target sequence is a promoter sequence.

Pomerantz et al teach the design of a polynucleotide encoding an artificial transcription factor comprising zinc fingers 1 and 2 of Zif268, and the Oct-1 homeodomain (e.g. paragraph bridging pages 93-94). Pomerantz et al teach that the artificial transcription factor expressed from the polynucleotide is capable of binding to a hybrid DNA binding site with the sequence 5'-AAATNNTGGGCG-3' *in vitro* (e.g. page 93, paragraph bridging columns; Figure 3). To determine whether the DNA binding protein could function *in vivo* Pomerantz et al fused the polynucleotide encoding the artificial transcription factor DNA binding domain to a VP16 transcription activation domain to create a polynucleotide encoding ZFHD1-VP16, which was inserted into an expression vector, and cotransfected into 293 cells with a reporter construct (e.g. page 95, paragraph bridging middle and right columns). The reporter constructs taught by Pomerantz et al contain a promoter comprising two copies of the hybrid DNA binding sites (e.g. page 95, paragraph bridging middle and right columns). Further, Pomerantz et al teach that the assays were conducted *in vivo* to determine whether the fusion protein could specifically regulate gene expression and can be used with other engineered proteins (e.g. page 95, right column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the polynucleotide and target sequence of Green et al to include the VP16 activation domain and the location of the target site in the promoter as taught by Pomerantz et al because Green et al and Pomerantz et al teach it is within the ordinary skill in the art to engineer

an artificial transcription factor and study the binding of the transcription factor to its cognate DNA binding site.

One would have been motivated to make such a modification in order to receive the expected benefit of determining whether the modified zif268 transcription factor taught by Green et al is capable of specifically binding its target sequence *in vivo*. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 22 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Green et al (Biochem J., Vol. 333, pages 85-90, 1998; see the entire reference) in view of Pomerantz et al (Science, Vol. 267, No. 5194, pages 93-96, 1995; see the entire reference) as applied to claims 25, 36 and 39-41 above, and further in view of Guyer et al (Genetics, Vol. 149, pages 633-639, 1998; see the entire reference). This rejection was made in the Office action mailed 6/14/2006 and is reiterated below.

The combined teachings of Green et al and Pomerantz et al are described above and applied as before.

Green et al and Pomerantz et al do not teach the polynucleotide comprising a maize C1 activation domain and do not teach a plant cell comprising the target sequence.

Guyer et al teach *Arabidopsis* plants comprising a stably integrated hybrid transcription factor, and plants comprising an activatable transgene, where the hybrid transcription factor and activatable transgene are brought together in the same cell by fertilization (e.g. paragraph

bridging pages 633-634). Specifically, Guyer et al teach a GAL4 DNA binding domain fused to a maize C1 transcription activation domain as the hybrid transcription factor, and a reporter transgene controlled by a synthetic promoter comprising ten GAL4 DNA binding sites (e.g. paragraph bridging pages 633-634; Figure 1). Further, Guyer et al teach that many positive transcriptional regulatory factors are modular, consisting of a DNA-binding domain and an activation domain and that fusing combinations of these elements derived from different kingdoms results in the production of diverse hybrid factors having defined DNA-binding specificity and transcriptional activation function with advantages over expression under direct control by a natural promoter (e.g. page 633, left column; page 638, paragraph bridging columns).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the polynucleotide and target sequence of Green et al to include the VP16 activation domain and the location of the target site in the promoter as taught by Pomerantz et al because Green et al and Pomerantz et al teach it is within the ordinary skill in the art to engineer an artificial transcription factor and study the binding of the transcription factor to its cognate DNA binding site. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the polynucleotide to comprise a C1 activation domain taught by Guyer et al and to use a plant cell comprising the modified zif268 cognate DNA binding site because Green et al and Pomerantz et al teach it is within the ordinary skill in the art to engineer an artificial transcription factor and study the binding of the transcription factor to its cognate DNA binding site and Pomerantz et al and Guyer et al teach it is within the ordinary skill of the art to test transcription factor DNA binding *in vivo* in a cultured cell.

One would have been motivated to make such a modification in order to receive the expected benefit of determining whether the modified zif268 transcription factor taught by Green et al is capable of specifically binding its target sequence *in vivo* in a plant cell thus expanding the number of species in which the modified zif268 transcription factor can be used. Further, one would be modified to use the modified mammalian zif268 DNA binding domain in a plant cell because Guyer et al teach that proteins from different kingdoms may be combined to create hybrid transcription factors for use in plants, and that these hybrid transcription factors may provide specific gene activation in plants. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 25, 36, 39-41 and 55 is rejected under 35 U.S.C. 103(a) as being unpatentable over Green et al (Biochem J., Vol. 333, pages 85-90, 1998; see the entire reference) in view of Barbas, III et al (US Patent No. 6,242,568, cited as reference A39 on the IDS filed 5/11/2005; see the entire reference). This rejection was made in the Office action mailed 6/14/2006 and has been extended to claim 53, which was amended to delete the term "pharmaceutical" from the preamble in the reply filed 10/17/2006.

The teachings of Green et al are described above and applied as before.

Green et al do not teach the polynucleotide further comprising a fourth zinc finger, wherein the zinc fingers are fused to an activation domain. Green et al do not teach the location of target site located within a promoter. Green et al do not specifically teach the use of a pharmaceutically acceptable excipient.

Barbas, III et al teach polynucleotides encoding zinc finger binding polypeptide variants, including expanded polypeptides (e.g. column 8, lines 55-60). The variant polypeptides encoded by the polynucleotides of Barbas, III et al bind to either DNA or RNA and may enhance or suppress transcription from a promoter. Barbas, III et al teach that "expanded" proteins are zinc finger polypeptides to which additional zinc finger modules have been added (e.g. column 7, lines 25-40). Examples of proteins that may be expanded include TFIIIA and zif268 (e.g. column 7, lines 49-55). Further, Barbas, III et al teach that the expanded zinc finger proteins may also be mutagenized (e.g. column 7, lines 20-55). Barbas, III et al teach that expanded zinc finger domain polypeptides comprising 2 to 12 zinc fingers derived from Zif268 can be fused to the leucine zipper domains of the Jun/Fos proteins, and may further include activation domains to produce activators of transcription (e.g. Example 12). Further, Barbas, III et al teach that these heterodimeric Zif constructs are advantageous since they allow for extended palindromic sequences (e.g. Example 12). Further, Barbas, III et al teach that the isolated zinc finger polynucleotide can be formulated in a pharmaceutically acceptable excipient for delivery to cells (e.g. column 23, line 55 to column 24, line 60; column 19, lines 12-50).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the polynucleotide encoding the zinc finger polypeptide of Green et al to include up to 12 zinc fingers, a leucine zipper and an activation domain as taught by Barbas, III et al because Green et al and Barbas, III et al teach it is within the ordinary skill in the art to engineer Zif268 zinc finger proteins. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to provide the target site for the protein of Green and Barbas, III et al in a promoter because Barbas, III et al teach it is within the skill of

the art to activate transcription from a promoter. Moreover, it would have been obvious to one of ordinary skill in the art to formulate the polynucleotide in a pharmaceutically acceptable excipient, because Green et al and Barbas, III et al teach the production of zinc finger polynucleotides and Barbas, III et al teach the formulation of the polynucleotide in a pharmaceutically acceptable excipient for delivery to cells.

One would have been motivated to make such a modification in order to receive the expected benefit of being able to activate gene transcription from an extended palindromic sequence in a promoter as taught by Barbas, III et al. This would allow one to activate transcription more specifically from a sequence that occurs less frequently in a genome of a cell than the shorter binding site taught by Green et al. Furthermore, one would have been motivated to use a pharmaceutically acceptable excipient to deliver the polynucleotide to reduce toxicity to the cell due to the solution carrying the polynucleotide. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments - 35 USC § 103

With respect to all rejections of record under 35 U.S.C. 103, Applicant's arguments filed 10/17/2006 have been fully considered but they are not persuasive. The response asserts that the secondary references do not cure the deficiency of Green et al with regard to the limitation where the isolated polynucleotide must encode a protein that is "engineered to bind to a target sequence." This is not found persuasive, because the teachings of Green et al meet that specific

limitation for the reasons set forth above. For these reasons, and the reasons made of record in the previous office actions, the rejections are maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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PRIMARY EXAMINER